UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/494,212	01/25/2000	Shi-Lung Lin	USP9768A-EI	3155

7590 10/31/2003

Raymond Yat Chiu Chan
1050 Oakdale Ln
Arcadia, CA 91006

EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/494,212	LIN ET AL.	
	Examin r	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2003 and 21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-18,20,22,23,25,26 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-18,20,22,23,25,26 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 18 March 2003 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 7-18, 20, 22, 23, 25, 26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

> possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

4. For purposes of examination, the claimed methods have been interpreted as encompassing the generation of only full-length cDNAs and mRNAs, performing an infinite number of cycles of amplification, and the addition of DNA and RNA polymerases but a single time for any number of cycles of amplification.

5. Page 10, last paragraph, teaches that one must add RNA polymerase "in every round of transcription due to the denaturation step." Accordingly, the specification does not reasonably suggest that applicant was in possession, at the time of filing, of methods where RNA polymerase is added but a single time or any number of cycles of amplification.

6. Claims 1-3, 7-18, 20, 22, 23, 25, 26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*,

> *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

7. For purposes of examination, the method of said claims has been interpreted as encompassing the production of mRNA of any length, where said mRNA has secondary structures, and where virtually any DNA or RNA polymerase can be used.

8. The specification has been found to set forth the following five examples.

   a. Example 1, page 13: "Cell Fixation and Permeabilisation."

   b. Example 2, pages 13-14: "First Reverse Transcription and Polynucleotide Tailing of the First-Strand cDNAs"

   c. Example 3, page 14: "Denaturation, Double-stranded cDNA Synthesis and Transcriptional Amplification"

   d. Example 4, page 15: "Second Reverse Transcription, Denaturation, Double-Stranded cDNA Synthesis and mRNA Amplification"

   e. Example 5, page 16: "Amplification Cycling Procedure"

9. The above-cited example, however, do not teach the skilled artisan how to overcome art-recognized problems and difficulties.

10. The claimed method clearly requires the use of a RNA polymerase so to generate a plurality of full-length mRNA. However, the use of RNA polymerase is not without difficulties. US Patent Publication 2003/0087275 teaches:

> [0051] The TATA box or the like, which may be comprised in the DNA sequence for regulating transcription of the invention can be found in various species ranging from simple eukaryotes such as baker's yeast to more complex organisms such filamentous fungi and humans. The TATA box assists in directing RNA polymerase (RNA polymerase 11) to the downstream mRNA initiation site. The RNA polymerase binds to regions of DNA, i.e., the RNA polymarase [*sic*] binding site often in general referred to as a promoter. The TATA box is in most cases necessary for transcription because the RNA polymerase normally cannot recognize the initiation sites on its own. The TATA box directs the RNA polymerase to the m RNA initiation site once the RNA polymerase has bound to the TATA box. Yet another problem occurs when the RNA polymerase scans for the TATA box. The RNA polymerase cannot recognize the TATA box on its own. It has to use (a) transcription factor(s) to find the TATA box. After the transcription factor(s) bind(s) to the TATA box, then the RNA polymerase can recognize and bind to the TATA box. Then the RNA polymerase binds to the transcription factor(s), which identify the TATA box. The TATA box then guides the RNA polymerase to the mRNA initiation site where transcription can begin. (Emphasis added)

The claimed method does not require any TATA box to be present in the cDNA, or any transcription factors be used. As shown above, both are required in order for the RNA polymerase to bind to the appropriate site on the cDNA such that transcripts are produced.

11. US Patent Publication 2003/0040099 teaches:

> [0015] However, successful generation of highly infectious cDNA clones has often been problematic due to the presence of mutations in the virus RNA template population caused by the inherent mutability of RNA viruses, the relatively low fidelity of the DNA polymerases used in cDNA synthesis, instability and toxicity of viral sequences in bacterial hosts, and the infidelity of the RNA polymerases used for in vitro transcriptions. (Emphasis added)

The specification is essentially silent as to how one of skill in the art is to be overcome the issue of fidelity. Assuming *arguendo*, that only full-length amplicons are produced, the specification is silent as to how the skilled artisan would be able to recognize those amplicons that have an

incorrect sequence over that of one, which is correct. Accordingly, one may well produce "full length" mRNA, yet the sequence no longer encodes the intended protein, or any protein, if a mutation, e.g., substitution, occurs early on in the sequence.

12. US Patent 6,303,306 B1 states:

> Amplification efficiency is high in the amplification system based on replicated RNA. However, because of a poor heat stability of conventional enzymes, namely RNA dependent DNA polymerase, DNA dependent RNA polymerase and DNA dependent DNA polymerase, the reaction temperature does not have to be high, and non-specific hybridization between the nucleic acid as a template and the primer cannot be avoidable, so that decrease of the specificity is a problem. In addition, the instability of the enzymes creates a severe problem in supplying and storing enzymes, and storage in a frozen state or in a refrigerator is required. (Emphasis added)

With non-specific hybridization taking place, one may well achieve priming of the incorrect sequence. Additionally, the incorrectly primed sequence as well as the correctly primed sequence can give rise to further erroneous amplicons/transcripts when one considers the aspect of infidelity of the polymerases, be they DNA or RNA.

13. The claimed method also is considered to encompass the incorporation of fluorescently labeled nucleotides. However, the art recognizes that such nucleotides cannot be incorporated in RNA produced via a DNA dependent RNA polymerase. In support of this position, attention is directed to US Patent 6,140,053, which states:

> Another problem, which still needs to be resolved, is that DNA/RNA polymerases, which are able to use the four fluorescently labeled NTPs instead of the unmodified counterparts, have not been identified.

14. Yet another problem confronting RT-PCR is when the mRNA contains secondary structures. In support of this position, attention is directed to US Patent Publication 2003/0180737, which states:

> RNA molecules with secondary structure may be poorly represented in cDNA libraries. Populations of RNA with secondary structure may also yield cDNA libraries with a short insert size. Furthermore, RNA molecules containing secondary structure may be difficult to detect in assays such as reverse transcription-polymerase chain reaction (RT-PCR). (Emphasis added)

15. Attention is also directed to column 40 of Jones (US Patent 5,858,671), which teaches at length of the problems associated with enzymatic coupling efficiency and accuracy of nucleotides. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant levels. For example, during oligonucleotide synthesis of a 70-mer, requiring 69 couplings, a 99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ($0.99^{69} = 0.50$)." In the present case, applicant is claiming a product that would be the result of an infinite number of couplings, not just 69 as described above.

While a disclosure is not required to teach each and every embodiment encompassed by the claims, the specification, "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the" invention. The record clearly indicates that the invention is drawn to an area of technology replete with art-recognized difficulties. The instant disclosure, however, is essentially silent as to how one is to ensure that they obtain only full-length cDNA such that full-length mRNA is ultimately transcribed from the amplified cDNA population. The failure of the instant disclosure to fully enable the claimed invention unfairly and inappropriately shifts the burden of enablement from applicant to that of the public. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

Here, however, the level of enabling disclosure provided does not vary inversely with the degree of unpredictability of the factors involved. The shifting of the burden of enablement is unfair and level of experimentation required for he public to practice the full breadth of the claimed invention is undue. Accordingly, and in the absence of convincing evidence to the contrary, claims 1-3, 7-18, 20, 22, 23, 25, 26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1-3, 7-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claim 1 is indefinite with respect to just what constitutes "using polymerase reaction activity." "Polymerase" is an enzyme that can have an "activity," but "polymerase reaction" is a process, not an enzyme. Accordingly, it is not clear how a process has an "activity." Claims 2-3, 7-18, and 20, which depend from claim 1, fail t overcome this issue and are similarly rejected.

19. Claim 11 is indefinite with respect to the endpoints of the range in temperatures. As presently worded, only one end-point of the range is identified.

20. Claims 12 and 33 are indefinite with respect to what constitutes "Tth-like DNA polymerases."

21. Claim 22 is indefinite with respect to what constitutes "polynucleotide-ended complementary DNAs." A "complementary DNA, or cDNA, is comprised of a plurality of nucleotides, *id est*, a polynucleotide. Consequently, it is not clear how a polynucleotide-ended cDNA is any different from any other cDNA. Claims 23, 25, 26, and 29-35, which depend from claim 22, fail to overcome this issue and are similarly rejected.

22. Claims 11 and 33 are indefinite as a result of usage of the abbreviation "C. therm." Applicant is urged to use the full name at the first occurrence in a series of claims.

Conclusion

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

25. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
10/28/2003